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Intracranial aneurysms and delayed cerebral ischemia: Decades of evidence on unexplored event

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ABSTRACT

Background: The current literature reveals a female predominance among delayed cerebral ischemia (DCI) cases and speculates the fluctuations in sex-specific hormones as an explanation for the disparity. We aimed to address the following simple question: Do older females undergoing unruptured aneurysm (UA) treatment have higher chances for DCI?

Materials and methods: We conducted a literature search of PubMed, Scopus, and Web of Science from 1980 to 2024. We identified studies on evident DCI in patients who underwent treatment for UA and additionally provided another DCI case following surgery in a patient with a UA. We pooled all evidence and examined sex differences using Bayesian hierarchical models with 4 chains of 4,000 Markov Chain Monte Carlo samples.

Results: Of the 5,293 publications identified, 43 were selected for the full-text review. Sixteen case series were eligible for inclusion. Modelled DCI posterior mean odds ratio (OR) was 2.4 (0.4-17.8) and 0.4 (0.1-2.3) for females and males, respectively, with posterior probabilities of 87% and 17%, respectively, for the OR exceeding 1.0.

Conclusion: Our findings suggest females have a substantially greater risk for DCI, which suggests a potential impact of sex-specific hormonal variations, further justifying the observed predominance. Furthermore, we suspect that prolonged drying of the exposed vessels contributes to the onset of DCI.

Keywords: cerebral blood flow, cerebrovascular disease, neurosurgery, neurobiology, cerebral ischemia, vasospasm

INTRODUCTION

Intracranial aneurysms occur in up to 2% of the general population and cause approximately 85% of subarachnoid hemorrhages (SAHs) [1, 2]. Surgical clipping and endovascular coiling are considered to be the most common procedures employed to prevent rupture of an aneurysm [3]. Although these procedures are widely accepted as effective modalities, they are associated with various complications including intracerebral hemorrhage, cardio-cerebrovascular events, status epilepticus, systemic infection, and occasionally delayed cerebral ischemia (DCI).

At present, DCI following procedures for unruptured aneurysms (UAs) is of particular interest given its rare occurrence and unknown pathogenesis. It is characterized by narrowing of at least one intracranial artery due to contraction of the smooth muscle in the vessel wall [4]. Typically, the spasm occurs within hours to weeks following surgery, and a delayed onset offers a potential window for the prevention [4, 5].

Despite some improvements in the management of ischemia over the last few decades, it remains a significant predictor of the treatment outcomes of UAs. However, given the exceptional and possibly underreported number of incidents, it is no wonder that all existing evidence is limited, and most of the hypotheses are suggested based on limited evidence.

Current literature reveals a predominance of age (> 50 y.o.) female patients with DCI after treatment for UAs. Although intracranial aneurysms are more prevalent in females [6], the impact of menopausal age on both UAs and surgical outcomes is yet to be thoroughly studied [7]. Despite the value of detailed medical data on metabolic abnormalities and comorbid diseases, studies are lacking information on this matter. Acknowledging the crucial role of estrogen levels in the physiology of blood vessels [2, 8, 9], fluctuations (e.g., menstrual cycles, climacteric) in sex-specific hormones could explain the sex disparity in DCI. One possible theory is that vaso-protective effects diminish in postmenopausal women with a higher DCI risk. We hypothesized that such hormonal variations could affect DCI onset. In the context of limited data,

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we wish to answer the simple question: Does being an older female recipient increase the chance of DCI in patients undergoing UA treatment?

Considering the limited body of evidence and the sparse occurrence of DCI, the literature still needs to be updated. Here, we present another case of DCI following an extracranial double (STA-MCA) bypass with Sylvian fissure dissection. Notably, neither clipping nor coiling was performed. Therefore, we can temporarily set aside most of the aforementioned theories. We aimed to provide the first DCI case in a patient with an intracranial aneurysm unexposed to the aforementioned procedures. This approach may provide more reliable estimates and facilitate the development of a new meta-analytic technique.

MATERIALS AND METHODS

Study Design and Data Sources

We performed a systematic review and Bayesian multilevel regression analysis of case series reporting DCI as a complication in treated UAs. To collect data for analysis, we searched for studies in the English language reporting on DCI cases in patients with UAs in the Scopus, Web of Science, and PubMed databases from January 1980 to May 2024. We conducted a comprehensive and standardized search using a broad range of keywords related to vasospasm, delayed ischemia, surgical procedures, and intracranial aneurysms. The full details of the search strategies are provided in **Appendix A** and **Appendix B**. We ensured consistency across databases and manually screened the bibliographies of all full-text articles corresponding to our criteria as well as review articles for additional citations. The final search results were updated until May 2024 to include the latest publications available.

We included studies that reported de novo DCI in patients undergoing surgical treatment for aneurysms without hemorrhage, and duplicate cases were excluded. We excluded articles that analyzed DCI following aneurysmal SAH. Conference abstracts were not included because of insufficient details.

Abstract Screening and Data Extraction

The review protocol was registered with PROSPERO, and the PRISMA guidelines were followed to conduct a systematic review [10]. Three reviewers participated in the selection of studies for inclusion in this analysis. First, RA conducted a systematic literature search and gathered relevant publications. Subsequently, AS and BC independently reviewed the abstracts and full-text articles to identify eligible studies for the final analysis. We managed all references using Endnote Online, and a standardized data collection form was developed in the MS Office. When available, we recorded data for publication date, patient sociodemographic characteristics (sex and age), aneurysm location, postoperative day of DCI onset, treatment modalities, smoking status, comorbid diseases, intradural operation time, and metabolic abnormalities. Any disagreements in data extraction were reconciled by a review of the full text. The inclusion and exclusion process of the studies in the review is illustrated in the PRISMA flow diagram (**Figure 1**, **Appendix C**, and **Appendix D**). The Joanna Briggs Institute (JBI) tool was used to assess the risk of bias in each case reports [11]. The JBI consists of ten questions in the checklist to evaluate the relevance of the studies, identify potential biases, and test the quality of the review.

Statistical Analysis

We performed all the statistical analyses in R-Studio (version 4.2.3). Our primary interest was sex-related effect size in patients undergoing treatment for UAs. We pooled all information from the publications into one data frame and performed a regression analysis. Patients without reported DCI were coded as the comparison group [12]. Given the absence of differentiating formalization between early and delayed DCI [2], all participants were categorized into binary outcomes (DCI or non-DCI). The events-per-predictor ratio was 14:1, which was assumed to meet a “rough guide” to prevent overfitting. Bayesian multilevel regression models were fitted using the probabilistic language Stan to estimate the DCI risk (odds ratio [OR]) with a specific emphasis on sex-specific coefficients. Analyses were performed using the “brms” package [13], which defines non-informative priors as the default for all model parameters. This approach ensures that the results are primarily driven by data rather than by subjective prior beliefs. For the model, four chains of 4,000 Markov Chain Monte Carlo (MCMC) samples were retrieved. The first 800 samples were discarded as warm-up. Model convergence was assessed using R-hat diagnostic statistics, effective sample size statistics, and trace plots. The degree of nesting was measured using the intraclass correlation coefficient (ICC).

RESULTS

A literature search yielded 5,293 references. We eliminated 2,468 duplicates, leaving 2,825 distinct references for screening. After screening, 43 full texts were left for a thorough review, with 11 additional citations identified by a manual search of references and a supplementary search (**Figure 1**). Following a review of full texts, 16 case series [2, 12, 14-27] reporting DCI onset following surgeries in patients with UAs were included in the review and quantitative analysis. In total, these articles report 29 total DCI cases, including the present case, and 21 non-DCIs.

Bias assessment revealed a satisfactory methodological quality in the included studies. The most common limitation was the absence of statistical analysis. The median (interquartile range) age of the study population was 56.0 (48-67), with a mean 53.4. When analyzing the DCI cases separately, the median age was 55.0 (47-63), while the mean age was 53.5 years. The median age of non-DCIs was 54 (49-57), with a mean age of 53.3. The publication years ranged from 1980 to 2020, and most of the studies were published in 2020 (31%). **Figure 2** shows speculation regarding the onset of DCI in the selected studies. Detailed characteristics of the included studies are provided in the **Appendix E**, **Appendix F**, and **Appendix G**. The 16-case series included reported DCI cases in 28 patients who underwent surgical procedures to treat UAs, with the postoperative day of DCI onset ranging from 1 to 29. Most series did not report comorbidities, intradural operation time, smoking status, or metabolic abnormalities. The most frequently suggested causal pathways are shown in **Figure 2**.

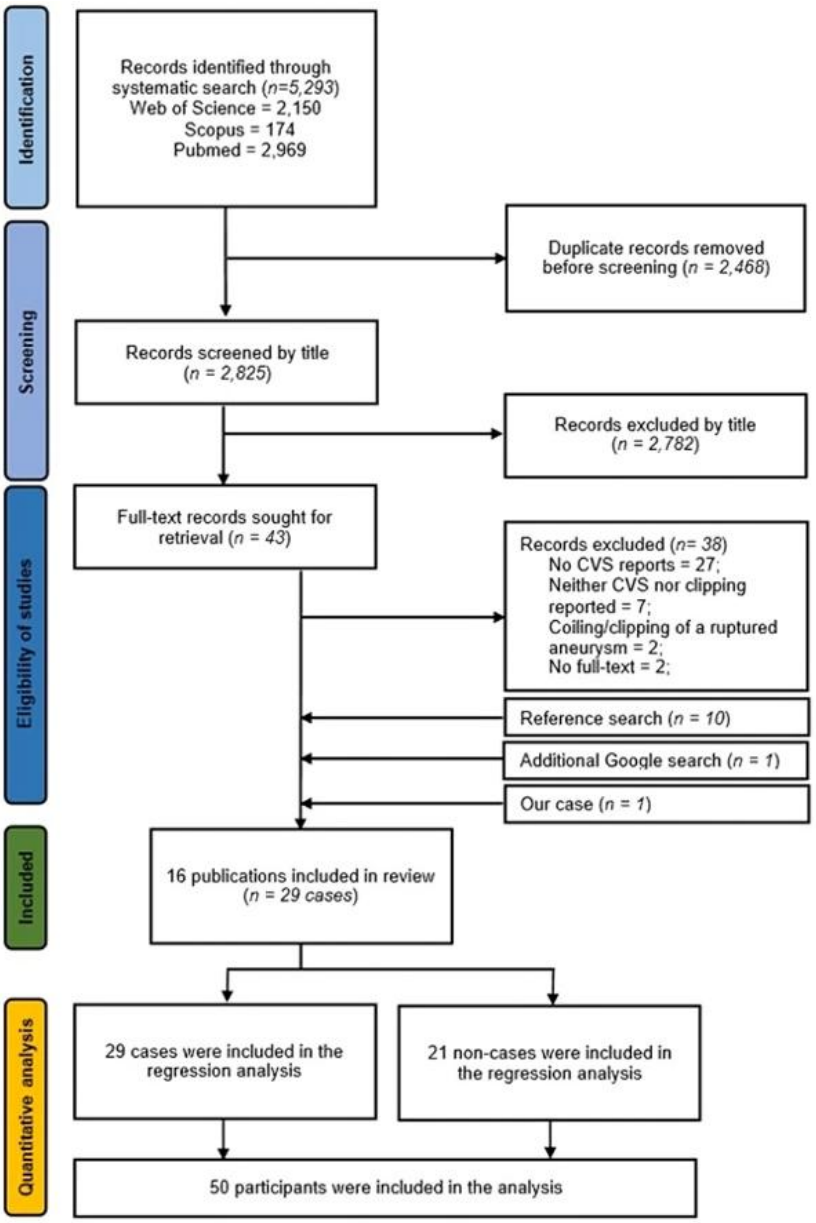

Figure 1. Selection of studies for inclusion (Source: Authors' own elaboration)

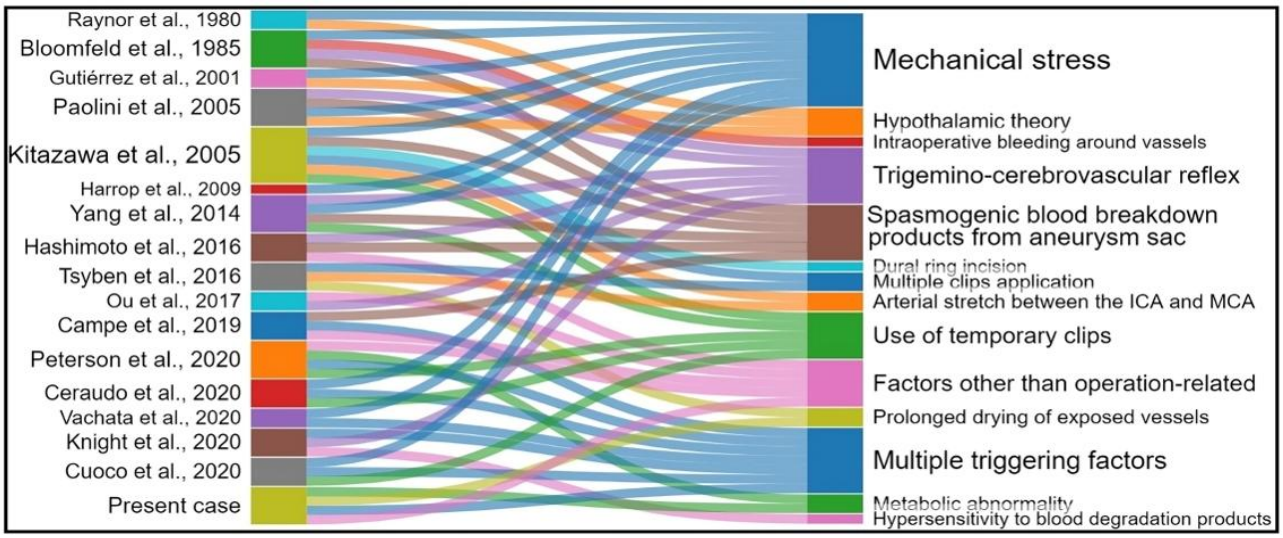

Figure 2. Potential causal mechanisms for cerebral vasospasms (Source: Authors' own elaboration)

Case Presentation

A female patient aged 67 years old with a medical history of hypertension and diabetes was referred to the emergency department due to severe noise in the head, dizziness, and headaches for an extended period of time. Neurological examination was normal, and computed tomography angiography (CTA) revealed an incidental 12 × 9 mm aneurysm with a wide neck at the left middle cerebral artery (MCA) bifurcation. After discussion, the patient opted to replace the extracranial-intracranial double-barrel superficial temporal artery (STA)–MCA bypass with endovascular trapping of the M1-M2 segment. Following general anesthesia and positioning in 3-point cranial fixation, palpation was performed to map the course of the STA. A linear incision was then made over the parietal branch of the STA, and a smaller non-contiguous satellite incision was made over the frontal branch of the STA. After dissection, the branches of the STA were clipped proximally and flushed with heparinized saline solution. Right pterional craniotomy was performed. Microdissection was carried out from distal to proximal to open the Sylvian fissure, followed by dissection and exposure of the M2 segments of the MCA. Each donor vessel was cut to an appropriate length, and the surrounding adventitia was cleared. Once the recipient vessels were prepared by dissection, each end-to-side anastomosis was performed from the STA donor to the MCA recipient using an interrupted 10-0 suturing technique. The patient tolerated the procedure well and was transferred to the intensive care unit under stable sedation. On postoperative day 1, the patient presented with headache and emesis. CTA revealed ischemia of the right temporal lobe pole (**Appendix H**). Cerebral angiography showed significant narrowing of all branches of the right MCA compared to the preoperative CTA. The patient remained in the critical care unit and received 100 mg of nimodipine and aspirin daily. After four days, her condition improved, and the clinicians decided to perform partial endovascular coiling of the aneurysm. Eventually, the patient fully recovered and was discharged without neurological deficits.

Regression Analysis

Bayesian regression analysis consisted of 50 observations from selected studies. The mean ORs for both sexes were calculated (**Figure 3**). Unfortunately, much of the valuable information was missing from these publications. Therefore, adjustments were made to the participants' age and sex. Relying on the estimates, posterior DCI risk was substantially higher for female sex (OR 2.42; 95% confidence interval: 0.43-17.82) than that for male sex (OR 0.41; 95% confidence interval: 0.06-2.33). Alternatively, the probability of exceeding the null value (OR 1.0) for the modelled risks was reported to be 83% and 17% for females and males, respectively. The R-hat diagnostic statistic was equal to 1.00, the effective sample size statistic exceeded 2,000 for all parameters, and visual inspection of the trace plots revealed stationarity across chains (**Appendix I**), indicating good model convergence.

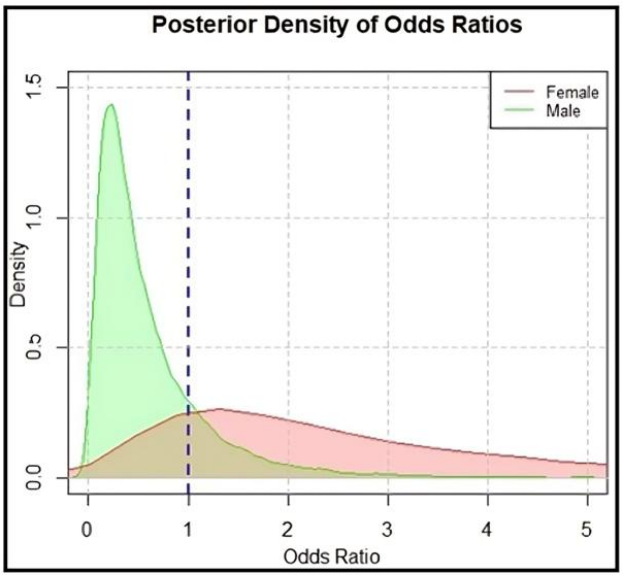

Figure 3. The risk estimates for females and males adjusting for age (Source: Authors' own elaboration)

DISCUSSION

Although there are several reviews available narratively synthesizing DCI case studies, the rare and underreported DCI occurrence justifies frequent updates on poorly explored complications. Existing literature shows a female predominance in the DCI population [6, 16, 23]. Such a discrepancy might be partially rationalized by the higher prevalence of UAs in females [22], but the limited number of patient reports does not allow us to make a clear statement on this matter [22].

The neurobiology of postsurgical DCI in UAs is poorly understood. A long-standing hypothesis assumes mechanical stress as a cause, while others vary from the hypothalamic theory to metabolic abnormalities. In the latest review [2], while highlighting the vasodilatory effect of estrogen, the authors questioned whether other sex-specific factors might contribute to DCI onset and suggested the need to evaluate whether such factors contribute. Similarly, given the female sex superiority and our case features, we hypothesized a possible impact of hormonal variations.

Systematic Review

To our knowledge, this is the largest review of electively treated UAs complicated with DCI. Most studies were conducted in the USA (38%), Italy (12%), and Japan (12%). The Republic of Korea, Germany, the UK, the Czech Republic, Brazil, and China accounted for 38% of the total. Of the patients with DCI (n = 29), 79% were females. In terms of location, aneurysms were left-sided, right-sided, and bilateral in 59%, 34%, and 7% of cases, respectively. In terms of non-DCI, females comprised the majority (62%), and aneurysms were mostly on the left (52%), right (43%), and bilaterally located (5%).

Among the included publications, DCI incidents varied from 1 to 30 days, with a suggested latency period ranging from 1 to 29 days. The most frequently observed neurological abnormalities included aphasia, hemiparesis, headache, and disorientation, whereas facial droop, seizures, Gerstmann syndrome, and coma were less common. The most frequently suggested causal pathways to DCI include mechanical stress, followed by "multiple triggering factors," spasmogenic blood breakdown products from the aneurysm sac, trigemino-cerebrovascular reflex, and use of temporary clips and so forth. It is worth noting that most of these hypotheses dwarf each other, further highlighting the complexity of DCI neurobiology. However, incident DCIs in patients with UAs seem to challenge

most hypotheses. Nevertheless, causal paths cannot be identified beyond proposing and supporting certain hypotheses and further updates are required in this field.

Case Presentation

We present a case of DCI following extracranial double bypass surgery with Sylvian fissure dissection in a patient with a UA in the left MCA (M1 and M2). The DCI presented on the first postoperative day and was accompanied by headache and vomiting.

To our knowledge, this is the first report of post-extracranial bypass vasospasm in a patient with a UA. Since no common aneurysm treatment procedure was performed, we can place aside most of the living theories behind DCI. We believe that factors unrelated to the procedure could result in the onset of DCI. Although the patient underwent continuous suction with saline solution of vessels, prolonged drying caused by the microscope's thermal energy could also contribute to DCI onset, which was also suspected previously [22]. In addition, we were curious about the potential involvement of sex-related hormonal factors that play a role in causing the complication. This requires more thorough investigation in future primary studies.

Unlike the more commonly reported DCI cases, this report highlights a rare complication after complex bypass surgery, which notably deviates from conventional cases in which DCI is typically associated with SAH. This allowed us to consider potential underlying factors unrelated to direct aneurysm treatment, such as the thermal effects of microscopic equipment and prolonged vessel exposure during surgery. These aspects have rarely been considered in the existing literature, which commonly attributes DCI to mechanical or hemodynamic shifts. The onset and specific circumstances of DCI differ from those of typical presentations, highlighting the potential influence of sex-related hormonal factors and unique surgical considerations. This distinction emphasizes the need for broader investigations of DCI's complex etiology of DCI, particularly in surgical cases where traditional risk models may not be fully applicable.

Regression Analysis

Among the included publications, only one study provided a quantitative analysis [12]. This study identified a statistical association between multiple clip placement, temporary clipping, and postsurgical DCI. However, no other significant differences were observed in the other variables. The authors have not reported any metabolic abnormalities.

Normally, case series are highly prone to systematic errors, and as a consequence, cases are strictly selected and do not represent the target population. Hence, such a bias could result in a spurious association. In our regression analysis, 30 of 50 observations (60%), as well as 9 (31%) of DCI cases, came from a single study [12]. This potentially violates the crucial assumption of conventional regression independence. Given the nesting structure, multilevel models would be a good approach to consider such dependency. Furthermore, it allows reasonable estimates even for groups with small sample sizes, which would be difficult using ordinal regression [28].

The estimates from the analysis suggested females had a 142% higher risk of post-surgical DCI, while the male sex were associated with a 59% lower risk after adjusting for age. In addition, the probability of null value exceedance (OR 1.0) for the modelled risks was 83% in females, whereas it was 17% for males. Our estimates correspond to existing evidence regarding sex-specific differences in the surgical treatment of UAs.

Assuming that sex-specific hormonal differences impact DCI incidence, sex was the primary interest. Our model included a low proportion of males in our models. Although this raises a problem in statistical inference [28], intracranial aneurysms are naturally more prevalent in females [6, 7, 23]. Therefore, such observations may reflect actual UAs in the population. In addition, we performed both Bayesian analysis and MCMC sample retrieval based on a single-level approach as a sensitivity model (**Appendix J**). While the effect size differed slightly, the exceedance probability of the threshold value changed noticeably (92% for females and 8% for males). Finally, considering the hierarchical nature of the dataset (ICC = 0.75), we report on the multilevel model estimates. It would be interesting to merge the data frame with individual data, test it, and discuss its reliability in future studies.

Strengths and Limitations

To the best of our knowledge, this is the largest review to collect the greatest number of cases and encompass decades of evidence. An additional strength of this study is that it is the first report of DCI following bypass surgery in a patient with a UA. Furthermore, we included a Bayesian framework that provides a reliable strategy to analyze such limited data and cope with uncertainty related to the variance. As a result, it allowed us to provide a pilot quantitative analysis, considering all available evidence from case reports.

This study has several limitations. All information was collected from a case series with a limited number of patient reports and patient characteristics. Although Bayesian framework allowed us to implement weak priorities for predictors, which may reduce bias due to unmeasured confounding [29], our regression analyses could not adjust for other essential variables (except age); hence, our findings regarding potential causal pathways are exploratory and require further evaluation. Future studies should focus on the clinical and medication history, and other potential confounders that might be important in the analysis of the underlying causes of DCI. A key limitation of the DCI research literature is the spurious perception and latency period. Therefore, there may be unreported cases, and cases that developed later than the patient follow-up period may have led to selection bias. Finally, there is still a need for empirical research to clearly generate hypotheses. The causal pathways underlying these associations require clarification by primary studies that measure the temporal relationships between metabolic abnormalities (e.g., hormonal differences, hyperglycemia, hypoxemia, and hyperlipidemia) and DCI.

CONCLUSION

This systematic review included data spanning over 40 years. UA-related DCIs are rare, and evidence is extremely limited. When occurring in a delayed fashion following surgical treatment of UAs, it should be preventable. Our findings suggest that females are at a substantially greater risk for DCI, possibly driven by sex-specific hormonal factors. Furthermore, we suspect that prolonged drying of the exposed vessels contributes to the onset of DCI. Therefore, additional research is needed to explore this interplay and propose ideas about causal pathways.

Author contributions: RA: conception, design of the work, analysis; **BC:** design of the work and substantive revision; **AS:** acquisition, drafted the work; **RK:** acquisition, drafted the work; **CN:** acquisition, drafted the work; **CP:** conception and substantive revision; **AG:** study concept and design, interpretation of data, drafting of manuscript. All authors have agreed with the results and conclusions.

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Ethical statement: The authors stated that the study does not require any ethical approval. It is a review of existing literature.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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APPENDIX A

Table A1. Search strategy identify studies reporting on the vasospasm occurrence in the post-surgical cohort

Database	Access date	Search terms
PubMed (1965-2024) 2,969	5th December, 2023	((cerebral vasospasm) OR (unruptured aneurysm)) AND ((vascular neurosurgery) OR (elective clipping))
Web of Science (1990-2024) 2,150	5th December, 2023	((cerebral vasospasm) OR (unruptured aneurysm)) AND ((vascular neurosurgery) OR (elective clipping))
Scopus (1979-2024) 174	5th December, 2023	((cerebral vasospasm) OR (unruptured aneurysm)) AND ((vascular neurosurgery) OR (elective clipping))

APPENDIX B

Table B1. Excluded studies (n = 38)

ID	PY	Author	Title	Excluded
1	2015	Alan et al.	Impact of age on 30-day postoperative outcome of surgery for ruptured and unruptured intracranial aneurysms	No CVS/DCI reports
2	2024	Baykara et al.	Middle cerebral artery ischemic complications after flow diverter deployment from internal carotid artery extending into M1 segment	No CVS/DCI reports
3	2014	Bekelis et al.	Predicting inpatient complications from cerebral aneurysm clipping: The nationwide inpatient sample 2005-2009: Clinical article	No CVS/DCI reports
4	2015	Bekelis et al.	New York State: Comparison of treatment outcomes for unruptured cerebral aneurysms using an instrumental variable analysis	Neither CVS/DCI nor clipping were reported
5	2017	Bekelis et al.	Comparison of clipping and coiling in elderly patients with unruptured cerebral aneurysms	No CVS/DCI reports
6	2017	Bekelis et al.	The impact of hybrid neurosurgeons on the outcomes of endovascular coiling for unruptured cerebral aneurysms	Neither CVS/DCI nor clipping were reported
7	2019	Bhogal et al.	Treatment of unruptured, saccular, anterior choroidal artery aneurysms with flow diversion: A single centre experience	No CVS/DCI reports
8	2022	Catapano et al.	A comparative propensity-adjusted analysis of microsurgical versus endovascular treatment of unruptured ophthalmic artery aneurysms	No CVS/DCI reports
9	2015	Chen et al.	Surgical treatment of patients with unruptured intracranial aneurysms	No CVS/DCI reports
10	2019	Chikamatsu et al.	A rare case of an unruptured aneurysm arising from the proximal end of the fenestration of the infracallosal segment (A2) of the anterior cerebral artery	No CVS/DCI reports
11	2018	Choque-Velasquez et al.	Double-clip technique: An effective clipping technique for small and very small aneurysms	No CVS/DCI reports
12	2012	Chovanes et al.	The predominance of metabolic regulation of cerebral blood flow and the lack of “classic” autoregulation curves in the viable brain	Neither CVS/DCI nor clipping were reported
13	2014	Chua et al.	An unruptured anterior communicating artery aneurysm with bilateral infraoptic anterior cerebral arteries. Case report and review of the literature	Neither CVS/DCI nor clipping were reported
14	2014	Consoli et al.	Endovascular treatment of unruptured and ruptured brain arteriovenous malformations with onyx18: A monocentric series of 84 patients	No CVS/DCI reports
15	1980	Cooper et al.	Preoperative arteriographic spasm and outcome from aneurysm operation	Neither CVS/DCI nor clipping were reported
16	2022	Diana et al.	Microsurgical clipping versus newer endovascular techniques in treatment of unruptured anterior communicating artery-complex aneurysms: A meta-analysis and systematic review	No CVS/DCI reports
17	1995	Dix et al.	Ruptured and unruptured intracranial aneurysms–Surgical outcome	No CVS/DCI reports
18	2015	Eto et al.	Unruptured cerebral aneurysm associated with fenestration of the anterior cerebral artery successfully treated with coil embolization using an intracranial stent: A case report	Neither CVS/DCI nor clipping were reported
19	2011	Eto et al.	Treatment of unruptured saccular vertebral artery aneurysm for preservation of the parent artery for advanced age people: A case report	No CVS/DCI reports
20	2023	Garg et al.	Endovascular coiling versus neurosurgical clipping for treatment of ruptured and unruptured intracranial aneurysms during pregnancy and postpartum period	No CVS/DCI reports
21	2023	Gaub et al.	Evolution of open surgery for unruptured intracranial aneurysms over a fifteen year period-increased difficulty and morbidity	No CVS/DCI reports
22	2018	Hernández-Durán et al.	The application of the unruptured intracranial aneurysm treatment score: A retrospective, single-center study	No CVS/DCI reports
23	2015	Jalbert et al.	Clipping and coiling of unruptured intracranial aneurysms among medicare beneficiaries, 2000 to 2010	No CVS/DCI reports
24	2015	Jo et al.	Treatment outcomes of surgical clipping for unruptured anterior circulation aneurysm-single institute experiences in the era of neurophysiologic monitoring and endovascular treatment	No CVS/DCI reports
25	2016	Kai et al.	Treatment of unruptured duplicated middle cerebral artery aneurysm: Case report	No CVS/DCI reports
26	1998	Leber et al.	Intracranial aneurysms: A review of endovascular and surgical treatment in 248 patients	No CVS/DCI reports
27	2010	Mascarenhas et al.	Unexpected angiographic and visual findings after clipping of a carotid-ophthalmic aneurysm	Clipping of a ruptured aneurysm
28	2020	Moon et al.	Result of coiling versus clipping of unruptured anterior communicating artery aneurysms treated by a hybrid vascular neurosurgeon	No CVS/DCI reports
29	1999	Morizane et al.	Endovascular surgery for untreated ruptured aneurysm with symptomatic vasospasm	Coiling of a ruptured aneurysm
30	2014	Mukerji et al.	Temporary clipping for unruptured aneurysms	No CVS/DCI reports
31	2016	Nakagomi et al.	Clipping surgery for unruptured middle cerebral artery aneurysms	No CVS/DCI reports

Table B1 (Continued). Excluded studies (n = 38)

ID	PY	Author	Title	Excluded
32	2022	Nussbaum et al.	Procedural complications in patients undergoing microsurgical treatment of unruptured intracranial aneurysms: A single-center experience with 1923 aneurysms	No CVS/DCI reports
33	2005	Santoro et al.	Vasospasm of venous grafts in extra-intracranial by-pass. Report of two cases	Neither CVS/DCI nor clipping were reported
34	2005	Suyama et al.	Surgical treatment of unruptured cerebral aneurysms in the elderly	No CVS/DCI reports
35	2003	Vilalta et al.	Late vasospasm in aneurysm of intracranial carotid bifurcation	No full text
36	2002	Wanke et al.	Endovascular treatment of unruptured intracranial aneurysms	No CVS/DCI reports
37	2022	Winter et al.	Clipping of unruptured cerebral aneurysms: Are older patients at higher risk?	No CVS/DCI reports
38	2023	Yang et al.	Long-term outcomes of surgical clipping of saccular middle cerebral artery aneurysms: A consecutive series of 92 patients	No full text

Note. PY: Publication year

APPENDIX C

Table C1. PRISMA 2020 for abstract checklist

Section and topic	Item #	Checklist item	Reported (yes/no)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Not applicable
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No specific funding
Registration	12	Provide the register name and registration number.	Yes

APPENDIX D

Table D1. PRISMA 2020 checklist [10]

Section and topic	Item #	Checklist item	Location where item is reported (page)
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for abstracts checklist.	**Appendix C**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	**Appendix A**
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4-5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Not applicable
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4-5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4-5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4-5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4-5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6, **Figure 1**
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	**Appendix B**

Table D1 (Continued). PRISMA 2020 checklist [10]

Section and topic	Item #	Checklist item	Location where item is reported (page)
Study characteristics	17	Cite each included study and present its characteristics.	**Appendix C**
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Not applicable
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-10
	23b	Discuss any limitations of the evidence included in the review.	10-11
	23c	Discuss any limitations of the review processes used.	10-11
	23d	Discuss implications of the results for practice, policy, and future research.	11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	This study was registered with PROSPERO, identifier CRD42023488611).
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	No specific funding.
Competing interests	26	Declare any competing interests of review authors.	Authors declare no competing interests.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: Template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	No new data is generated

APPENDIX E

Table E1. Detailed characteristics of the included articles (n = 16) and the present case

No	Author (year)	Country	Sex	Age	AL	Symptoms	VPOD	Treatments	Deficits	TC	D	H	SL	OC	SH	MA
1	Raynor et al. (1980) (1)	USA	Female	25	Left ICA	Ptosis & headache	1	NA	Hemiparesis	No	NA	NA	NA	NA	NA	NA
2	Bloomfield and Sonntag 1985 (2)	USA	Female	54	Right MCA	Left hemiparesis	9	Hypervolemia & dexamethasone	Weakness	No	NA	NA	NA	NA	NA	NA
3	Gutiérrez et al. (2001)(3)	Brazil	Female	55	Left ICA	Chronic headache	1	Vasodilator (papaverine)	Hemisparesis, aphasia, & coma	No	NA	NA	NA	NA	NA	NA
4	Paolini et al. (2005) (4)	Italy	Female	47	Right MCA bifurcation	Left hemiparesis	28	Hypervolemia & antiplatelet	None	No	NA	NA	NA	NA	Yes	NA
5	Kitazawa et al. (2005) (i) (5)	Japan	Female	53	Left paraclinoid carotid	Aphasia	9	Hypertension, hypervolemia, & hemodilution	None	No	NA	NA	240 min	NA	NA	No
6	Kitazawa et al. (2005) (ii) (5)	Japan	Female	21	Left paraclinoid carotid	Aphasia & Gerstmann syndrome	12	Hypertension, hypervolemia, & hemodilution	None	Yes	NA	NA	180 min	NA	NA	No
7	Kitazawa et al. (2005) (iii) (5)	Japan	Female	63	Left side*	Aphasia & hemiparesis	3	NA	NA	Yes	NA	NA	NA	NA	NA	NA
8	Kitazawa et al. (2005) (iv) (5)	Japan	Female	62	Left side*	Aphasia	16	NA	NA	Yes	NA	NA	NA	NA	NA	NA
9	Kitazawa et al. (2005) (v) (5)	Japan	Female	59	Left side*	Aphasia & hemiparesis	3	NA	NA	No	NA	NA	NA	NA	NA	NA
10	Kitazawa et al. (2005) (vi) (5)	Japan	Male	57	Left side*	NA	11	NA	NA	No	NA	NA	NA	NA	NA	NA
11	Kitazawa et al. (2005) (vii) (5)	Japan	Female	52	Right side*	NA	11	NA	NA	No	NA	NA	NA	NA	NA	NA
12	Kitazawa et al. (2005) (viii) (5)	Japan	Female	39	Right side*	Convulsion	5	NA	NA	No	NA	NA	NA	NA	NA	NA
13	Kitazawa et al. (2005) (ix) (5)	Japan	Male	29	Right side*	NA	11	NA	NA	No	NA	NA	NA	NA	NA	NA
14	Harrop et al. (2009) (i) (6)	USA	Female	38	Left ICA	Aphasia & right hemiparesis	7	Hypertension, hypervolemia, & hemodilution	None	No	NA	NA	NA	NA	NA	NA
15	Harrop et al. (2009) (ii) (6)	USA	Female	39	Bilateral MCA	Aphasia	1	Hypertension, hypervolemia, & hemodilution	None	No	NA	NA	NA	NA	NA	NA
16	Yang et al. (2014) (i) (7)	Republic of Korea	Female	61	Left MCA bifurcation	Aphasia, mental status changes	10	Picardipine, hydration, & antiplatelet	Partial aphasia	Yes	NA	NA	NA	NA	NA	NA
17	Yang et al. (2014) (ii) (7)	Republic of Korea	Female	41	Left ICA	Aphasia & right facial numbness	28	Nicardipine, hydration, & antiplatele	Partial aphasia	Yes	NA	NA	NA	NA	NA	NA
18	Tsyben et al. (2016) (i) (8)	UK	Female	53	Left MCA bifurcation	None	2	Hypertension & hypervolemia	Dysphasia & hemiparesis	No	NA	NA	NA	NA	NA	NA
19	Tsyben et al. (2016) (ii) (8)	UK	Male	70	Left MCA bifurcation	None	2	Hypertension, hypervolemia, & hemodilution	Dysphasia & hemiparesis	No	Yes	Yes	NA	NA	NA	NA
20	Hashimoto et al. (2016) (9)	Japan	Female	62	Left ICA	Headache, aphasia, &right hemiplegia	11	Hypervolemia & antiplatelet	Acalcula & paraphasia	No	NA	NA	NA	NA	NA	NA
21	Ou et al. (2017) (10)	China	Male	50	Right MCA	Headache, aphasia & left hemiparesis	10	Nimodipine, hypervolemia, antiplatelet, &hyperbaric O_2	Weakness	No	NA	NA	NA	NA	NA	NA

Table E1 (Continued). Detailed characteristics of the included articles (n = 16) and the present case

No	Author (year)	Country	Sex	Age	AL	Symptoms	VPOD	Treatments	Deficits	TC	D	H	SL	OC	SH	MA
22	Campe et al. (2019) (11)	Germany	Female	69	Right MCA bifurcation	Aphasia & left hemiparesis	12	Nimodipine, antiplatelet	None	No	NA	NA	NA	NA	NA	NA
23	Peterson et al. (2020) (12)	USA	Female	67	Right MCA bifurcation	Syncopal episode	29	Anti-epileptic medications & vasolidators (nimodipine & verapamile)	Hemiparesis & dysarthria	Yes	Yes	Yes	NA	NA	NA	NA
24	Ceraudo et al. (2020) (13)	Italy	Female	59	Left MCA bifurcation	Headache & dizziness	1	Vasodilator (nimodipine)	Aphasia & hemiparesis	Yes	No	Yes	NA	NA	Yes	NA
25	Vachata et al. (2020) (i) (14)	Czech Republic	Female	65	Left MCA bifurcation	None	5	Vasodilator (nimodipine)	Aphasia & epileptic seizures	No	No	Yes	NA	NA	No	NA
26	Vachata et al. (2020) (ii) (14)	Czech Republic	Male	72	Right MCA bifurcation	None	6	Vasodilator (nimodipine)	Aphasia, disorientation	No	No	Yes	NA	NA	No	NA
27	Knight et al. (2020) (15)	USA	Male	68	Middle anterior communicating artery aneurysm	None	5	Vasodilator (nicardipine)	Facial droop, dysarthria, & aphasia	No	NA	NA	NA	NA	NA	NA
28	Cuoco et al. (2020) (16)	USA	Female	53	Left MCA bifurcation	NA	13	Vasolidators (nimodipine & verapamile)	Hemiparesis & seizures	Yes	NA	NA	NA	Yes	NA	NA
29	Present case	Kazakhstan	Female	67	Left MCA bifurcation	Headcahe & vomiting	1	Vasolidators (nemodipine) & aspirin	Headache (vomiting	No	Yes	Yes	NA	No	No	No

Note. *: No details; POD: Post-operative day; NA: Not available; IOT: Intradural operation time; AL: Aneurysm location; VPOD: Vasospasm POD; TC: Temporal clips; D: Diabetes; H: Hypertension; SL: Surgery length or IOT; OC: Any other comorbidities; SH: Smoking history; & MA: Metabolic abnormalities (hypoglycemia or hypoxia)

APPENDIX F

Table F1. Detailed characteristics of non-cases [12]

No	Author (year)	Sex	Age	AL	PS	DF	D	H	SL	OC	SH	MA
1	Kitazawa et al. (2005) (i)	Female	68	Left side*	Disorientaion	NA	NA	NA	NA	NA	NA	NA
2	Kitazawa et al. (2005) (ii)	Male	67	Left side*	NA	NA	NA	NA	NA	NA	NA	NA
3	Kitazawa et al. (2005) (iii)	Female	67	Right side*	NA	NA	NA	NA	NA	NA	NA	NA
4	Kitazawa et al., 2005 (iv)	Male	61	Left side*	NA	NA	NA	NA	NA	NA	NA	NA
5	Kitazawa et al. (2005) (v)	Female	59	Left side*	NA	NA	NA	NA	NA	NA	NA	NA
6	Kitazawa et al. (2005) (vi)	Male	57	Left side*	Agnosia & perseveration	NA	NA	NA	NA	NA	NA	NA
7	Kitazawa et al. (2005) (vii)	Female	57	Right side*	NA	NA	NA	NA	NA	NA	NA	NA
8	Kitazawa et al. (2005) (viii)	Male	56	Right side*	NA	NA	NA	NA	NA	NA	NA	NA
9	Kitazawa et al. (2005) (ix)	Female	56	Left side*	NA	NA	NA	NA	NA	NA	NA	NA
10	Kitazawa et al. (2005) (x)	Female	55	Left side*	NA	NA	NA	NA	NA	NA	NA	NA
11	Kitazawa et al. (2005) (xi)	Male	54	Left side*	NA	NA	NA	NA	NA	NA	NA	NA
12	Kitazawa et al. (2005) (xii)	Female	54	Right side*	NA	NA	NA	NA	NA	NA	NA	NA
13	Kitazawa et al. (2005) (xiii)	Female	54	Right side*	NA	NA	NA	NA	NA	NA	NA	NA
14	Kitazawa et al. (2005) (xiv)	Male	51	Left side*	NA	NA	NA	NA	NA	NA	NA	NA
15	Kitazawa et al. (2005) (xv)	Female	51	Right side*	Aphasia & Gerstmann syndrome	NA	NA	NA	NA	NA	NA	NA
16	Kitazawa et al. (2005) (xvi)	Male	49	Basilar artery aneurysm, & superior cerebellar artery aneurysm	NA	NA	NA	NA	NA	NA	NA	NA
17	Kitazawa et al. (2005) (xvii)	Female	49	Left side*	Gerstmann syndrome	NA	NA	NA	NA	NA	NA	NA
18	Kitazawa et al. (2005) (xviii)	Female	43	Right side*	NA	NA	NA	NA	NA	NA	NA	NA
19	Kitazawa et al. (2005) (xix)	Male	40	Right side*	NA	NA	NA	NA	NA	NA	NA	NA
20	Kitazawa et al. (2005) (xx)	Female	37	Right side*	NA	NA	NA	NA	NA	NA	NA	NA
21	Kitazawa et al. (2005) (xxi)	Female	35	Left side*	NA	NA	NA	NA	NA	NA	NA	NA

Note. *: No details; NA: Not available; AL: Aneurysm location; PS: Postoperative symptoms; DF: Deficits; D: Diabetes; H: Hypertension; SL: Surgery length or IOT; OC: Any other comorbidities; SH: Smoking history; & MA: Metabolic abnormalities (hypoglycemia or hypoxia)

APPENDIX G

Table G1. Characteristics of the participants at baseline

Characteristic	Cases (n = 29)	Controls (n = 21)	Total
Age-years	53.4 ± 13.7	53.3 ± 9.1	50 (100%)
Sex			
Female	23 (79.3%)	13 (61.9%)	36 (72.0%)
Male	6 (20.6%)	8 (38.1%)	14 (28.0%)
Aneurysm location			
BCA	1 (4.7%)		1 (2.0%)
Left	11 (52.4%)	17 (58.6%)	28 (56.0%)
MCA	0 (0.0%)	1 (3.4%)	1 (2.0%)
Right	9 (42.9%)	10 (34.5%)	19 (38.0%)

APPENDIX H

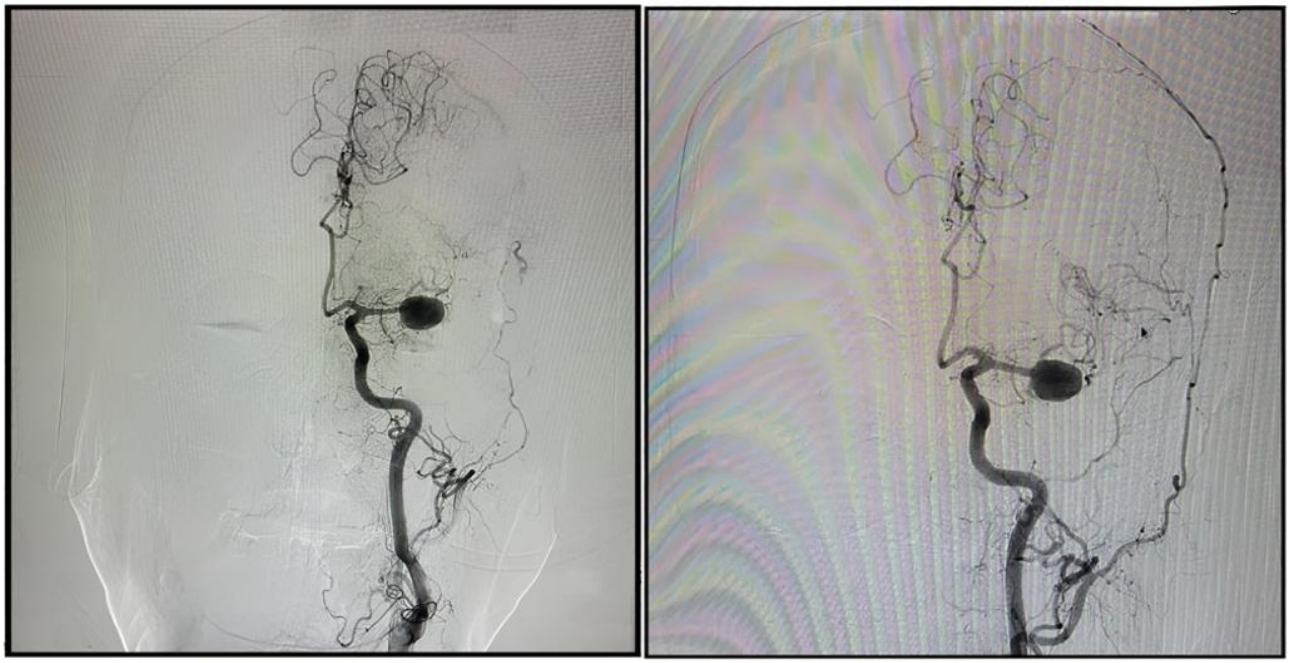

Figure H1. CTA on the first post-operative day represents the narrowing of all MCA branches (reprinted with permission of patient)

APPENDIX I

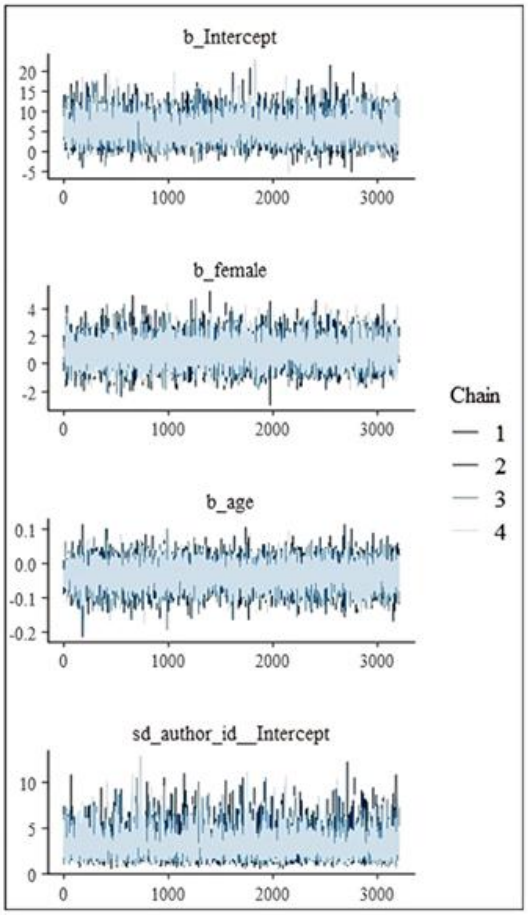

Figure I1. Trace-plot for model convergence (Source: Authors' own elaboration)

APPENDIX J

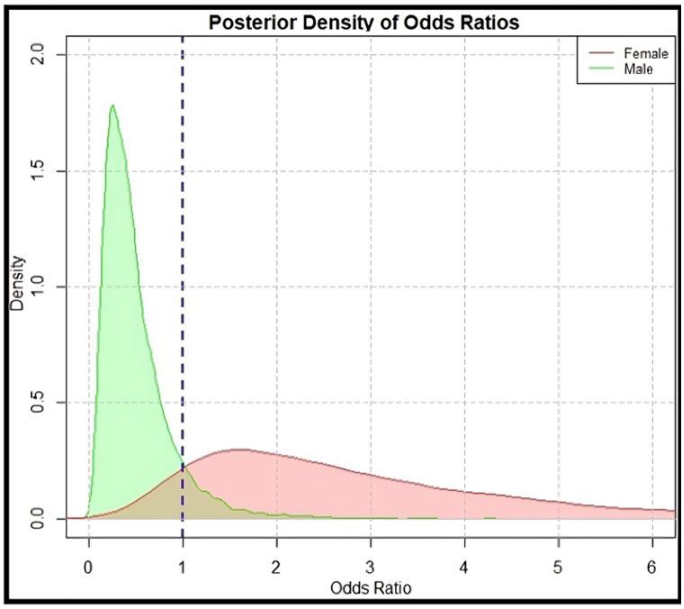

Figure J1. The risk estimates for females and males adjusting on age (single-level approach) (female OR: 2.52; 95% confidence interval: 0.66-9.88; male OR: 0.39; 95% confidence interval: 0.08-1.44; & probability of threshold exceedance: 92% for females & 8% for males) (Source: Authors' own elaboration)